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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/139,425	08/25/98	ESMON	UMRF-171

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EXAMINER
SANDALS, W

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 06/07/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.
09/139,425

Applicant(s)
Esmon et al.

Examiner
WILLIAM SANDALS

Group Art Unit
1636



☒ Responsive to communication(s) filed on Mar 21, 2000

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-25 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-13, 15-20, and 22 is/are rejected.

☒ Claim(s) 14, 21, and 23-25 is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 8

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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DETAILED ACTION

Response to Arguments

1. Amendments to the claims in Paper No. 10, filed March 21, 2000 have overcome the rejection of claims 1-12 under 35 USC 102, and 103 in the previous office action, and the rejections are withdrawn.
2. Arguments regarding the rejection of claims 5-7 and 16-19 under 35 USC 112, first paragraph are not found persuasive, and the rejection is sustained. Responses to the arguments are contained in the repeated rejection below.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 5-7 and 16-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of selectively delivering genes to a large vessel endothelial cell nucleus by binding a conjugate to an endothelial protein C receptor (EPCR).

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While applicants have shown the binding of a conjugate to an endothelial protein C receptor (EPCR) *in vitro*, they have not demonstrated any *in vivo* delivering of a gene to an endothelial cell, which constitutes a method of gene therapy. In order to do so, undue experimentation is required. Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors. Many of these factors have been summarized in *In re Wands*, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988).

The Wands factors as they apply to the instant claimed invention are as follows:

- a- The quantity of experimentation necessary to reduce the instant claimed invention to practice would involve delivering a gene to an endothelial cell for gene therapy.
- b- Only prophetic guidance and no examples of delivering a gene to an endothelial cell *in vivo* have been provided.
- c- The nature of the invention is complex. Gene therapy is a new and developing art as recited in Marshall in the section titled "The trouble with vectors", and at page 1054, column 3, and at page 1055, column 3. The problems of gene delivery, gene targeting to reach the intended host cell, and then to reach the intracellular target are not yet solved, as taught in Verma et al. (see especially page 239, column 3, the box titled "What makes an ideal vector?" and page 242).
- d- The prior art taught by Orkin et al. (see especially the section on "Gene transfer and expression" and "Gene therapy in man status of the field") described many problems in the developing field of gene therapy. Recited problems include: lack of efficacy, adverse short term effects and limited clinical experience, the inability to extrapolate experimental results and

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unreliability of animal models. Problems with the vector include: host immune response to the vector and the expressed product, difficulty of targeting the vector to the desired site, transient expression of the gene of interest and low efficiency of delivery of the vector to the targeted site.

e- The state of the art as taught by Verma et al., which states “the problems - such as the lack of efficient delivery systems, lack of sustained expression, and host immune reactions - remain formidable problems” and Anderson, W. F. (see page 25, top of column 1), which states “[e]xcept for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease”.

f- Therefore, given the analysis above, it must be considered that the skilled artisan would have needed to have practiced considerable non-routine, trial and error experimentation to enable the full scope of the claims.

Response to Arguments

5. Applicants have argued in Paper No. 5, that the argument above pertains to viral vectors. In as much as the references discuss viral vectors, those sections which are specific to the use of viral vectors for delivery of a nucleic acid to a cell clearly do not apply to the instant claimed invention. However, the bulk of the content of the references discusses the application of gene therapy, which does apply.

The statement in Anderson, WF, makes it clear that the state of the art in gene therapy, or delivery of nucleic acids for therapeutic purposes, is still a poorly understood art, and the references provided by applicant, while encouraging, do not overcome the problems facing

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practitioners in the gene therapy art, and make it clear that applicants must provide detailed teachings on how to make and use such an invention. Since these teachings are not presented in the instant claims and specification, the instant claimed invention is not enabled.

6. Paper No. 10 asserts that the amendments to the claims avoid the rejection. This is not the case, since the rejection is centered on the use of nucleic acids in a therapeutic method, for “gene therapy”. The claims and specification are not enabled for gene therapy, as set forth in the rejection above.

7. Paper No. 10 asserts that claims 7 and 19 have been rejected in error, since they are claiming “drugs and diagnostic agents”. The term of the claims, “drugs” is not defined, and as such, embraces the use of nucleic acids as “drugs”, which are not enabled (see above).

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claim 1 recites at lines 1-2 “delivering molecules to the nucleus of endothelium”.

Endothelium is a tissue, not a cell, and as such “endothelium” does not have a nucleus, per se.

Inserting the words “of a cell” into this phrase would cure this defect.

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11. Claim 1 recites at lines 5-6 "molecules are delivered to the nucleus of the large vessel endothelial cells where they are active". The phrase "where they are active" is unclear, since the word "they" may refer to the cells, or to the molecules.

12. Claim 1 is indefinite, since in line 6 it states "where they are active". What is meant by "active" here is unclear, since no antecedent basis for the word "active" occurs, and no definition of the word is set forth. "Active" may refer to any number of possibilities, and the word "active" infers some vague and undefined function.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

14. Claims 13, 15, 20 and 22 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No. 5,847,085.

US Pat No. 5,847,085 taught (see especially the summary) a conjugate of protein C which binds selectively to a EPCR, where the molecule is not a diagnostic agent, and where the conjugate may be delivered to a large vessel endothelial cell.

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Allowable Subject Matter

15. Claims 14, 21 and 23-25 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

16. Certain papers related to this application are *welcomed* to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

William Sandals, Ph.D.
Examiner
May 24, 2000


REMI VUCL, Ph.D.
PATENT EXAMINER